

Set	Items	Description
S1	1676	(EDB OR ED(N)B OR (FIBRONECT? (5N) DOMAIN?) OR ED-B) (50N) (ANTIBOD? OR MONOCLONAL? OR CHIMER? OR POLYCLONAL? OR IMMUNOG- LOB?)
S2	902	RD (unique items)
S3	185	S2/1999:2000
S4	717	S2 NOT S3
S5	631	S4 AND FIBRONECT?
S6	50	TARGET - S5
S7	581	S5 NOT S6
S8	50	TARGET - S7
S9	531	S7 NOT S8
S10	50	TARGET - S9
S11	481	S9 NOT S10
S12	50	TARGET - S11
S13	431	S11 NOT S12

?t s12/9/49

*DIACOG  
West  
9/00  
BR*

12/9/49 (Item 49 from file: 347)

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-2000/Nov W1  
 (c) format only 2000 Dialog Corporation

File 5:Biosis Previews(R) 1969-2000/Sep W3  
 (c) 2000 BIOSIS

File 73:EMBASE 1974-2000/Aug W2  
 (c) 2000 Elsevier Science B.V.

\*File 73: Update codes are currently undergoing readjustment.  
 For details type Help News73.

File 654:US Pat.Full. 1990-2000/Sep 12  
 (c) format only 2000 The Dialog Corp.

\*File 654: Reassignment data current through 12/06/1999 recordings.  
 Due to recent processing problems, the SORT command is not working.

File 71:ELSEVIER BIOBASE 1994-2000/Aug W4  
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File 349:PCT Fulltext 1983-2000/UB=20000907, UT=20000824  
 (c) 2000 WIPO/MicroPat

\*File 349: Phase 2 enhancements with current WIPO biblio data now online.  
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File 348:European Patents 1978-2000/Sep W02  
 (c) 2000 European Patent Office

File 35:Dissertation Abstracts Online 1861-2000/Jul  
 (c) 2000 UMI

\*File 35: File has resumed updating, see HELP NEWS 35.

File 357:Derwent Biotechnology Abs 1982-2000/Sep B2  
 (c) 2000 Derwent Publ Ltd

File 47:Gale Group Magazine DB(TM) 1959-2000/Sep 13  
 (c) 2000 The Gale group

File 50:CAB Abstracts 1972-2000/Aug  
 (c) 2000 CAB International

\*File 50: All year 2000 records have been reprocessed;  
 see HELP NEWS 50.

File 94:JICST-EPlus 1985-2000/May W1  
 (c)2000 Japan Science and Tech Corp(JST)

File 442:AMA Journals 1982-2000/Jul B1  
 (c)2000 Amer Med Assn -FARS/DARS apply

File 653:US Patents Fulltext 1980-1989  
 (c) format only 2000 The Dialog Corp.

\*File 653: Reassignment data current through 12/06/1999 recordings.  
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File 444:New England Journal of Med. 1985-2000/Aug W1  
 (c) 2000 Mass. Med. Soc.

File 143:Biol. & Agric. Index 1983-2000/Aug  
 (c) 2000 The HW Wilson Co

File 347:JAPIO Oct 1976-2000/Apr(UPDATED 000816)  
 (c) 2000 JPO & JAPIO

File 370:Science 1996-1999/Jul W3  
 (c) 1999 AAAS

File 44:Aquatic Sci&Fish Abs 1978-2000/Sep  
 (c) 2000 FAO (for ASFA Adv Brd)

File 77:Conference Papers Index 1973-2000/Jul  
 (c) 2000 Cambridge Sci Abs

File 342:Derwent Patents Citation Indx 1978-00/200042  
 (c) 2000 Derwent Info Ltd

\*File 342: File is now current.

File 10:AGRICOLA 70-2000/Sep  
 (c) format only 2000 The Dialog Corporation

File 457:The Lancet 1986-2000/Sep W2  
 (c) 2000 The Lancet, Ltd.

File 344:Chinese Patents ABS Apr 1985-2000/Aug  
 (c) 2000 European Patent Office

Set	Items	Description
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?ds

The inclusion of the type III repeat ED-B in the fibronectin molecule generates conformational modifications that unmask a cryptic sequence [published erratum appears in J Biol Chem 1993 Apr 5;268(10):7602]

Carnemolla B; Leprini A; Allemanni G; Saginati M; Zardi L

Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.

Journal of biological chemistry (UNITED STATES) Dec 5 1992, 267 (34) p24689-92, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9303

Subfile: INDEX MEDICUS

We have previously reported an anti-fibronectin monoclonal antibody (mAb) (BC-1) which reacts with an ED -B -containing beta-galactosidase-fibronectin fusion protein but not with an identical beta-galactosidase-fibronectin fusion protein in which the ED -B sequence is omitted. In further experiments aimed at localizing more precisely the epitope recognized by this mAb, we demonstrate that 1) the mAb BC-1 is indeed specific for ED-B-containing fibronectin (FN) molecules even though the epitope recognized by this mAb is localized on the type III homology repeat 7 (the one which precedes the ED-B sequence) and 2) in fibronectin molecules lacking the ED-B sequence, this epitope is masked. We further demonstrate that, to mask the epitope recognized by the mAb BC-1, the presence of at least half of the FN type III homology repeat 9 is necessary. We also report the production of the mAb IST-6 which recognizes only FN molecules in which the ED-B sequence is lacking. These data clearly demonstrate that the presence of the ED-B sequence within FN molecules generates conformational modification in the central part of the molecules that unmask previously cryptic sequences and masks others.

Tags: Human; Support, Non-U.S. Gov't

Descriptors: Antibodies, Monoclonal; \*Fibronectins --Chemistry--CH; \*Fibronectins --Genetics--GE; \*Protein

The fibronectin isoform containing the ED-B oncofetal domain: a marker of angiogenesis [published erratum appears in Int J Cancer 1995 Jul 4;62(1):118]

Castellani P; Viale G; Dorcaratto A; Nicolo G; Kaczmarek J; Querze G; Zardi L

Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.

International journal of cancer. Journal international du cancer (UNITED STATES) Dec 1 1994, 59 (5) p612-8, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9502

Subfile: INDEX MEDICUS

Different **fibronectin** (FN) isoforms are generated by the alternative splicing of 3 regions (ED-A, **ED -B** and IIICS) of the primary transcript. The FN isoform containing the **ED - B** sequence, a complete type-III-homology repeat, while having extremely restricted distribution in normal adult tissues, reveals high expression in fetal and tumor tissues. Using the **monoclonal antibody** (MAb) BC-I, specific for the FN isoform containing the **ED - B** sequence (B+.FN), we demonstrated here, using immunohistochemical techniques, that while this FN isoform is undetectable in mature vessels, it is highly expressed during angiogenesis both in neoplastic and in normal tissues, as in the case of the functional layer of endometrium during the proliferative phase. B+.FN is thus a marker for the formation of new vessels, and the BC-I MAb may be a useful reagent for evaluating the level of the angiogenetic process in different neoplasms.

Tags: Female; Human; Support, Non-U.S. Gov't

Design and use of a phage display library. Human antibodies with subnanomolar affinity against a marker of angiogenesis eluted from a two-dimensional gel.

Pini A; Viti F; Santucci A; Carnemolla B; Zardi L; Neri P; Neri D  
Dipartimento di Biologia Molecolare, Sezione di Biochimica, Universita'  
di Siena, 53'100 Siena, Italy.

Journal of biological chemistry (UNITED STATES) Aug 21 1998, 273 (34)  
p21769-76, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9811

Subfile: INDEX MEDICUS

We report the construction and the use of a phage display human antibody library ( $>3 \times 10^8$  clones) based on principles of protein design. A large repertoire of functional antibodies with similar properties was produced by appending short variable complementarity-determining region 3 (CDR3) onto the two antibody germ line segments most frequently found in human antibodies. With this strategy we concentrated sequence diversity in regions of the antibody structure that are centrally located in the antigen binding site, while leaving residues in more peripheral positions available for further mutagenesis aimed at improving the affinity of the selected antibodies. In addition, the library was tested by selecting antibodies against six biologically relevant antigens. Using only 0.3 microg of antigen eluted from a two-dimensional gel spot, we isolated binders specific for the ED-B domain of **fibronectin**, a marker of angiogenesis. These **antibodies** recognize the native antigen with affinities in the  $10(7)$ - $10(8)$  M-1 range, and perform well in immunosorbent assays, in two-dimensional Western blotting and in immunohistochemistry. The affinity of one anti-ED-B antibody was improved by 27-fold by combinatorially mutating six strategically selected residues in the heavy chain variable domain. A further 28-fold affinity improvement could be achieved by mutating residues 32 and 50 of the light chain. The resulting antibody, L19, bound to the ED-B domain of **fibronectin** with very high affinity ( $K_d = 54$  pM), as determined by real-time interaction analysis with surface plasmon resonance detection, band shift analysis, and by competition experiments with electrochemiluminescent detection.

Tags: Human; Support, Non-U.S. Gov't

**Fibronectin exposes different domains after adsorption to a heparinized and an unheparinized poly(vinyl chloride) surface.**

Yu JL; Johansson S; Ljungh A

Department of Medical Microbiology, University of Lund, Sweden.

Biomaterials (ENGLAND) Mar 1997, 18 (5) p421-7, ISSN 0142-9612

Journal Code: A4P

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9708

Subfile: INDEX MEDICUS

The adsorption of **fibronectin** to poly(vinyl chloride) catheters with end-point attached (EPA) heparin and tridodecylmethylammonium chloride-heparinized poly(vinyl chloride) was compared to that of unheparinized poly(vinyl chloride) using antibodies directed against four different domains of the protein. After perfusion of human plasma on the EPA-heparinized surface, the exposure of the N-terminal 29-kD fragment increased during the first 5 h of perfusion. Also, the exposure of the 30-kD gelatin-binding and 65-kD cell-binding fragments increased with time, but at a lower level. On the unheparinized catheter, low levels of antibodies bound to the different domains, and the binding showed little variation during the 5 h of plasma perfusion, indicating that the **fibronectin** molecule does not change configuration to a significant extent on this surface after the initial adsorption. When the EPA-heparinized surface was preabsorbed with human fibrinogen before incubation with **fibronectin**, significantly less of the 29-kD (fibrin-binding) domain was exposed, and the 30-kD domain was not exposed. Exposure of the 31- and 65-kD domains increased after preadsorption of fibrinogen to the surface. Since **fibronectin** has heparin-binding domains, it adsorbs differently to a heparinized versus an unheparinized surface. This will influence subsequent binding of other proteins to the surface, as well as potential binding of microbes. The use of **antibodies** to defined domains of the **fibronectin** molecule provides a powerful tool in studies of configurational changes of **fibronectin** after adsorption to different surfaces.

**Enzyme immunoassay of urinary fibronectin fragments in cancer patients with monoclonal antibodies specific for the cell binding domain of fibronectin.**

KATAYAMA MASAHIKO (1); HINO FUMITSUGU (1); KATO IKUNOSIN (1); MIYOSHI MASATO (2)

(1) Takarashuzo Yakuhinken; (2) Kyoto First Red Cross Hospital  
Igaku no Ayumi (Journal of Clinical and Experimental Medicine), 1989,  
VOL.150, NO.10, PAGE.695-696, FIG.1, TBL.1, REF.8

JOURNAL NUMBER: Z0649AAI ISSN NO: 0039-2359 CODEN: IGAYA

UNIVERSAL DECIMAL CLASSIFICATION: 616-006-071

LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan

DOCUMENT TYPE: Journal

ARTICLE TYPE: Short Communication

MEDIA TYPE: Printed Publication

ABSTRACT: Four monoclonal antibodies (FN4, FN9, FN10, and FN30) were generated against plasma **fibronectin** (FN). We measured urinary total FN levels in 32 cancer patients and 20 normal controls, using enzyme immunoassay (EIA) with monoclonal antibodies (FN30 and FN10) to the cell binding domain of FN. The total FN levels in patients with cancer increased significantly, as compared with those in normal controls. The FN fragments (100 and 65kDa) with the cell binding domain were found in the urine from patients with cancer, but not in the urine from normal controls. (author abst.)

DESCRIPTORS: **fibronectin** ; pathophysiology; human(primates); ce

Defining the topology of integrin alpha5beta1- fibronectin interactions using inhibitory anti-alpha5 and anti-beta1 monoclonal antibodies. Evidence that the synergy sequence of fibronectin is recognized by the amino-terminal repeats of the alpha5 subunit.

Mould AP; Askari JA; Aota Si; Yamada KM; Irie A; Takada Y; Mardon HJ; Humphries MJ

Wellcome Trust Centre for Cell-Matrix Research, School of Biological Sciences, University of Manchester, Manchester M13 9PT, United Kingdom.  
pmould@fs1.scq.man.ac.uk

Journal of biological chemistry (UNITED STATES) Jul 11 1997, 272 (28)  
p17283-92, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: GM47157, GM, NIGMS; GM49899, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9710

Subfile: INDEX MEDICUS

The high affinity interaction of integrin alpha5beta1 with the central cell binding domain (CCBD) of fibronectin requires both the Arg-Gly-Asp (RGD) sequence (in the 10th type III repeat) and a second site (in the adjacent 9th type III repeat) which synergizes with RGD. We have attempted to map the fibronectin binding interface on alpha5beta1 using monoclonal antibodies (mAbs) that inhibit ligand recognition. The binding of two anti-alpha5 mAbs (P1D6 and JBS5) to alpha5beta1 was strongly inhibited by a tryptic CCBD fragment of fibronectin (containing both synergy sequence and RGD) but not by GRGDS peptide. Using recombinant wild type and mutated fragments of the CCBD, we show that the synergy region of the 9th type III repeat is involved in blocking the binding of P1D6 and JBS5 to alpha5beta1. In contrast, binding of the anti-beta1 mAb P4C10 to alpha5beta1 was inhibited to a similar extent by GRGDS peptide, the tryptic CCBD fragment, or recombinant proteins lacking the synergy region, indicating that the RGD sequence is involved in blocking P4C10 binding. P1D6 inhibited the interaction of a wild type CCBD fragment with alpha5beta1 but had no effect on the binding of a mutant fragment that lacked the synergy region. The epitopes of P1D6 and JBS5 mapped to the NH2-terminal repeats of the alpha5 subunit. Our results indicate that the synergy region is recognized primarily by the alpha5 subunit (in particular by its NH2-terminal repeats) but that the beta1 subunit plays the major role in binding of the RGD sequence. These findings provide new insights into the mechanisms, specificity, and topology of integrin-ligand interactions.



A novel domain of fibronectin revealed by epitope mapping of a monoclonal antibody which inhibits fibroblasts-mediated collagen gel contraction.

Obara M; Yoshizato K

Hiroshima Laboratory of Yoshizato MorphoMatrix Project, ERATO, Japan Science and Technology Corporation, Kagamiyama, Higashihiroshima.

FEBS letters (NETHERLANDS) Jul 21 1997, 412 (1) p48-52, ISSN 0014-5793 Journal Code: EUH

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9711

Subfile: INDEX MEDICUS

The ability of cells to organize collagen fibrils is fundamental to a variety of processes found in embryogenesis, wound healing, fibrosis, and scar formation. We previously isolated a monoclonal antibody (mAb A3A5) which inhibits human fibroblast-mediated collagen gel contraction, an in vitro model producing the process of collagen morphogenesis. Human **fibronectin** (FN) has been shown to be the antigen of A3A5. The present study aimed at identifying the A3A5 epitope to reveal the mode of binding between collagen, FN, and fibroblasts in the process of gel contraction. The epitope was sought in FN fragments obtained by pepsin digestion and in recombinant FN fragments expressed in *Escherichia coli* by determining their immunological reactivity with A3A5, and was identified as a short segment consisting of the fourth through the amino half of the fifth FN type III. We propose a new functional domain of FN which plays a crucial role in the binding of fibroblasts to collagen fibrils and is involved in collagen morphogenesis.

Tags: Human

**Analyses of opsonic and monocyte adherence domains in a 180K MW human fibronectin fragment with monoclonal anti-fibronectin antibodies**

Czop, J.K.; Kadish, J.L.; Austen, K.F.

Harvard Med. Sch., MA, USA

American Society of Biological Chemists 75th Annual Meeting; American Association of Immunologists 68th Annual Meeting 8420056 St. Louis, MO (USA) 3-7 Jun 84

American Society of Biological Chemists (ASBC); American Association of Immunologists (AAI)

1984, Abstracts booklet available: Special Publications Dep., FASEB, 9650 Rockville Pike, Bethesda, MD 20814, USA, 2 vols.; Price: \$25.00 Paper No. 1011

Languages: ENGLISH

Descriptors: BIOCHEMISTRY; EXPERIMENTAL MEDICINE

Section Heading: BIOCHEMISTRY ; EXPERIMENTAL MEDICINE

Section Class Codes: 1500; 4500

**A study of measuring fibronectin concentration of the urine as a tumor marker.**

KATO TAKABUMI (1); NANBA MITSUO (1); SHIDA SHIGEMITSU (1)

(1) Dokkyo Univ. School of Medicine

Dokkyo Igakkai Zasshi (Dokkyo Igakukai Zasshi), 1991, VOL.6, NO.2,

PAGE.107-116, FIG.6, TBL.3, REF.18

JOURNAL NUMBER: L0104AAA ISSN NO: 0911-5900

UNIVERSAL DECIMAL CLASSIFICATION: 615.2.03:616-07 616-006-07

LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan

DOCUMENT TYPE: Journal

ARTICLE TYPE: Original paper

MEDIA TYPE: Printed Publication

**ABSTRACT:** The **fibronectin** value in urine (U-FN) was measured and the usefulness of U-FN as a marker for malignant tumor was investigated by enzymatic immunoassay using the **monoclonal antibody** specifically characterizing the **domain IV** of **fibronectin** (FN). Setting the cut off value at 200U/mgVcr, the positive rate obtained as follows; 8% of benign disease and 60% of malignant tumor. The positive rate obtained by CEA or CA19-9 is 40%. Therefore U-FN showed significantly better results than CEA and CA19-9. The result of combination assay was also satisfactory. In the staining of tissue, using the same monoclonal antibody, the cancerous tissue was more definitely stained than on the normal tissue. Experimental transplantation of gastric, colonic and liver metastatic tumor on nude mice were performed and recognized the increasing tendency of U-FN with the increase of size of tumor. Increasing mechanism of U-FN as well as its efficiency was investigated and was concluded that it was originated on the increasing of size of tumors. (author abst.)

**DESCRIPTORS:** human(primates); urine analysis;

**Presence of ED-A containing fibronectin in human articular cartilage from patients with osteoarthritis and rheumatoid arthritis.**

Chevalier X; Claudepierre P; Groult N; Zardi L; Hornebeck W

Department of Rheumatology, Hopital Henri-Mondor, Creteil, France.

Journal of rheumatology (CANADA) Jun 1996, 23 (6) p1022-30, ISSN 0315-162X Journal Code: JWX

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9702

Subfile: INDEX MEDICUS

**OBJECTIVE:** To determine whether normal (fetal and adult) and osteoarthritic (OA) and rheumatoid arthritic (RA) cartilage express a specific isoform of **fibronectin**, the extra **domain A** (ED-A) containing **fibronectin** (EDA+Fn). **METHODS:** Presence of **fibronectin** (EDA+Fn and native molecule) in cartilage matrix was studied using immunohistochemical assays with specific **monoclonal antibodies**. **Fibronectins** were identified by Western blots, in synovial fluids (SF) and cartilage extracts. **RESULTS:** EDA+Fn was either moderately present in the surface zone or undetectable in normal cartilage, while it was increased in OA cartilage surface. In one OA cartilage sample, EDA+Fn was localized in the matrix distant from the cartilage surface (patches of staining) and its presence was confirmed by immunoblotting. In RA cartilage EDA+Fn was present in the pericellular areas of the different layers. By Western blots, the presence of EDA+Fn was confirmed in OA SF (2/3) and RA SF (3/3) (with different patterns of fragmentation). **CONCLUSION:** EDA+Fn generally accumulates in the surface zone of OA cartilage, where it may play a role in extracellular matrix remodelling. Its presence was more abundant in SF and in cartilage from patients with RA.

Tags: Female; Human; Male

**Assay for human cellular fibronectin - using solid phase with affixed  
antibodies specific for extra type III domain of cellular fibronectin**

Patent Assignee: (SCRI-) SCRIPPS CLINIC & RE

Author (Inventor): PETERS J H; GINSBERG M H; COCHRANE C G

Patent (basic)

Patent No	Kind	Date	Examiner	Field of Search
US 4980279	A	901225	(BASIC)	

Derwent Week (Basic): 9103

Priority Data: US 852127 (860415)

Applications: US 852127 (860415)

Derwent Class: B04; D16; S03

Int Pat Class: G01N-033/53

Number of Patents: 001

Number of Countries: 001

Number of Cited Patents: 000

Number of Cited Literature References: 009

**Modulation of cell-adhesive activity of fibronectin by the alternatively spliced EDA segment.**

Manabe R; Ohe N; Maeda T; Fukuda T; Sekiguchi K

Research Institute, Osaka Medical Center for Maternal and Child Health, Japan.

Journal of cell biology (UNITED STATES) Oct 6 1997, 139 (1) p295-307, ISSN 0021-9525 Journal Code: HMV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9804

Subfile: INDEX MEDICUS

**Fibronectin** (FN) has a complex pattern of alternative splicing at the mRNA level. One of the alternatively spliced segments, EDA, is prominently expressed during biological processes involving substantial cell migration and proliferation, such as embryonic development, malignant transformation, and wound healing. To examine the function of the EDA segment, we overexpressed recombinant FN isoforms with or without EDA in CHO cells and compared their cell-adhesive activities using purified proteins. EDA+ FN was significantly more potent than EDA- FN in promoting cell spreading and cell migration, irrespective of the presence or absence of a second alternatively spliced segment, **EDB**. The cell spreading activity of EDA+ FN was not affected by **antibodies** recognizing the EDA segment but was abolished by **antibodies** against integrin alpha5 and beta1 subunits and by Gly-Arg-Gly-Asp-Ser-Pro peptide, indicating that the EDA segment enhanced the cell-adhesive activity of FN by potentiating the interaction of FN with integrin alpha5beta1. In support of this conclusion, purified integrin alpha5beta1 bound more avidly to EDA+ FN than to EDA- FN. Augmentation of integrin binding by the EDA segment was, however, observed only in the context of the intact FN molecule, since the difference in integrin-binding activity between EDA+ FN and EDA- FN was abolished after limited proteolysis with thermolysin. Consistent with this observation, binding of integrin alpha5beta1 to a recombinant FN fragment, consisting of the central cell-binding domain and the adjacent heparin-binding domain Hep2, was not affected by insertion of the EDA segment. Since the insertion of an extra type III module such as EDA into an array of repeated type III modules is expected to rotate the polypeptide up to 180 degrees at the position of the insertion, the conformation of the FN molecule may be globally altered upon insertion of the EDA segment, resulting in an increased exposure of the RGD motif in III10 module and/or local unfolding of the module. Our results suggest that alternative splicing at the EDA exon is a novel mechanism for up-regulating integrin-binding affinity of FN operating when enhanced migration and proliferation of cells are required.

Tags: Animal; Human; Support, Non-U.S. Gov't

Descriptors: Alternative Splicing; \* **Fibronectins** --Gene

**An improved method for quantification of extra domain A-containing cellular fibronectin (EDAcFN) in different body fluids.**

Ylatupa S; Mertaniemi P; Haglund C; Partanen P

Department of Clinical Chemistry, University of Helsinki, Finland.

Clinica chimica acta; international journal of clinical chemistry ( NETHERLANDS) Jan 31 1995, 234 (1-2) p79-90, ISSN 0009-8981

Journal Code: DCC

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9509

Subfile: INDEX MEDICUS

A quantitative direct enzyme immunoassay for the extra domain A-containing isoform of cellular **fibronectin** (EDAcFN) was established for screening of large series of blood samples and various body fluids of different pH and viscosity. The method is based on the **monoclonal antibody** DH1 recognizing the extra domain A in cellular **fibronectin** (EDAcFN). Studies on the effect of dilution of plasma and serum samples in this direct assay indicated that the measured concentration of cFN in the samples greatly depend on the ratio of sample dilution. The linearity of the assay was improved with sample dilution and the optimal dilution was 1:5. Stored diluted samples retained their cFN content at +4 degrees C, and -20 degrees C and -70 degrees C for months in contrast to samples stored undiluted. With this direct EIA the detection limit was 0.05 micrograms/ml and the linear portion of the standard curve could be extended above 30 micrograms/ml. Thus, the cFN concentration of blood samples could be measured reliably without inhibition also in samples with very high concentration of cFN. This is particularly important when measuring blood samples from cancer patients, since these samples may contain more than 20 micrograms/ml EDAcFN. The assay was standardized for blood samples but, due to the possibility of sample dilution, it also enabled reliable quantification of EDAcFN in various other body fluids. Undiluted some of the samples with non-neutral pH (urine, bile) or with high viscosity (seminal plasma) interfered with the assay. In addition to blood samples, the EDAcFN concentration was determined in samples of urine, bile, amniotic fluid, cervicovaginal secretions, seminal fluid, cerebrospinal fluid, bronchoalveolar lavage fluid, pleural fluid and saliva. Thereby, this modified method was shown to be applicable to various body fluids.

Tags: Female; Human; Support, Non-U.S. Gov't

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USPT	l17 and isoform	0	<u>L24</u>
USPT	l22 and nm	6	<u>L23</u>
USPT	l17 and (monoclonal or polyclonal or antibodies or antibody or igg or igm or immunoglobulin or antiserum or antisera or fab or scfv or chimeric)	10	<u>L22</u>
USPT	l19 and fibronectin.ti,ab,clm.	8	<u>L21</u>
USPT	l19 and fibronectin	40	<u>L20</u>
USPT	photolysis	2774	<u>L19</u>
USPT	l17 and (fibronectin or edb or ed-b)	0	<u>L18</u>
USPT	sn same l16	14	<u>L17</u>
USPT	chlorin	242	<u>L16</u>
USPT	cle6	1	<u>L15</u>
USPT	sn-cle6	0	<u>L14</u>
USPT	sn-cl-e6	0	<u>L13</u>
USPT	sncl6	0	<u>L12</u>
USPT	l4 same fibronectin	0	<u>L11</u>
USPT	l4 same l7	2	<u>L10</u>
USPT	l4 and l8	0	<u>L9</u>
USPT	(edb or ed-b or (domain near2 b)).clm.	137	<u>L8</u>
USPT	edb or ed-b or (domain near2 b)	1395	<u>L7</u>
USPT	l4 and fibronectin.clm.	3	<u>L6</u>
USPT	l1 and target	1	<u>L5</u>
USPT	PHOTOSENSITIZER? OR PHOTOLYSIS? OR PHOTODYNAMIC? OR PURPURINS? OR BENZOCHLORINS? OR PHOTOBLEACH? OR PHOTOBLEACH?	2437	<u>L4</u>
USPT	l1 and scfv	0	<u>L3</u>
USPT	l1 and monoclonal	0	<u>L2</u>
USPT	5,942,534.pn.	1	<u>L1</u>

**WEST**

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L21: Entry 3 of 8

File: USPT

Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5877289 A

TITLE: Tissue factor compositions and ligands for the specific coagulation of vasculature

## DEPR:

The SMPT cross-linking reagent, as with many other known cross-linking reagents, lends the ability to cross-link functional groups such as the SH of cysteine or primary amines (e.g., the epsilon amino group of lysine). Another possible type of cross-linker includes the heterobifunctional photoreactive phenylazides containing a cleavable disulfide bond such as sulfosuccinimidyl-2-(p-azido salicylamido) ethyl-1,3'-dithiopropionate. The N-hydroxy-succinimidyl group reacts with primary amino groups and the phenylazide (upon photolysis) reacts non-selectively with any amino acid residue.

## CLPR:

48. The binding ligand of claim 47, wherein said first binding region comprises an antigen binding region of an antibody that binds to VEGF/VPF, FGF, TGF.beta., a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor, hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF or TIMP.

## CLPR:

60. The binding ligand of claim 59, wherein said first binding region comprises VEGF/VPF, FGF, TGF.beta., a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor, hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF, TIMP or a soluble binding domain of a VEGF/VPF receptor.

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L21: Entry 3 of 8

File: USPT

Mar 2, 1999

US-PAT-NO: 5877289

DOCUMENT-IDENTIFIER: US 5877289 A

TITLE: Tissue factor compositions and ligands for the specific coagulation of vasculature

DATE-ISSUED: March 2, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX	N/A	N/A
Edgington; Thomas S.	La Jolla	CA	N/A	N/A

US-CL-CURRENT: 530/387.1; 530/381, 530/387.3, 530/387.7, 530/387.9, 530/388.1, 530/388.22, 530/388.85, 530/391.7, 530/391.9

## CLAIMS:

What is claimed is:

1. A binding ligand comprising:

(a) a first binding region that binds to a tumor cell, a component of tumor-associated vasculature or a component of tumor-associated stroma; the first binding region operatively linked to

(b) a Tissue Factor construct or a second binding region that binds to a Tissue Factor construct, wherein said second binding region comprises an antibody or an antigen binding region of an antibody.

2. The binding ligand of claim 1, wherein said Tissue Factor construct comprises a mutant Tissue Factor deficient in the ability to activate Factor VII.

3. The binding ligand of claim 2, wherein said Tissue Factor construct includes a mutation in the amino acid region between about position 157 and about position 167.

4. The binding ligand of claim 3, wherein, within said Tissue Factor construct, Trp at position 158 is changed to Arg; wherein Ser at position 162 is changed to Ala; wherein Gly at position 164 is changed to Ala; or wherein Trp at position 158 is changed to Arg and Ser at position 162 is changed to Ala.

5. The binding ligand of claim 1, wherein said Tissue Factor construct comprises a truncated Tissue Factor.

6. The binding ligand of claim 5, wherein said truncated Tissue Factor comprises amino acids 1 to about 219 of the mature Tissue Factor protein.

7. The binding ligand of claim 5, wherein said truncated Tissue Factor has the amino acid sequence of SEQ ID NO:23.

8. The binding ligand of claim 1, wherein said Tissue Factor construct comprises a first Tissue Factor or truncated Tissue Factor construct operatively linked to a second Tissue Factor or truncated Tissue Factor construct.

9. The binding ligand of claim 8, wherein said Tissue Factor construct comprises two truncated Tissue Factors.

10. The binding ligand of claim 9, wherein said Tissue Factor construct comprises three truncated Tissue Factors.

11. The binding ligand of claim 10, wherein said Tissue Factor construct comprises five truncated Tissue Factors.

12. The binding ligand of claim 8, wherein said Tissue Factor construct comprises a first and second Tissue Factor construct operatively linked via a disulfide, thioether or peptide bond.

13. The binding ligand of claim 1, wherein said Tissue Factor construct comprises a Tissue Factor construct with a hydrophobic membrane insertion moiety, and wherein said Tissue Factor construct is linked to said first binding region via a

PHOTODYNAMIC THERAPY FOR THE TREATMENT OF OSTEOARTHRITIS

PATENT NO.: 5,942,534  
ISSUED: August 24, 1999 (19990824)  
INVENTOR(s): Trauner, Kenneth, Sacramento, CA (California), US (United States of America)  
Hasan, Tayyaba, Arlington, MA (Massachusetts), US (United States of America)  
ASSIGNEE(s): The General Hospital Corporation, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)  
[Assignee Code(s): 10301]  
APPL. NO.: 8-948,623  
FILED: October 10, 1997 (19971010)

This application claims priority from U.S. Provisional application Ser. No. 60-028,198, filed on Oct. 10, 1996, which is incorporated herein by reference in its entirety.

This invention was made in part with government support under grant number DEFG02-91-ER61228 awarded by the Department of Energy. The United States government has certain rights in the invention.

FULL TEXT: 792 lines

...by clear bands against the blue background of the stained gelatin.

Example 1

Studies of **PDT** Efficiency Using Several Clinically Relevant Photosensitizers

Photosensitizer Effects on Chondrocyte Morphology

In the bright field and corresponding rhodamine fluorescence images of articular chondrocytes plated onto **fibronectin** -coated coverslips, the cells exhibited an overall polygonal to spheroid morphology and formed confluent monolayers...

Fibronectin receptor exhibits high lateral mobility in embryonic locomoting cells but is immobile in focal contacts and fibrillar streaks in stationary cells.

Duband JL; Nuckolls GH; Ishihara A; Hasegawa T; Yamada KM; Thiery JP; Jacobson K

Centre National de la Recherche Scientifique, Ecole Normale Supérieure, Paris, France.

Journal of cell biology (UNITED STATES) Oct 1988, 107 (4) p1385-96, ISSN 0021-9525 Journal Code: HNV

Contract/Grant No.: GM 29234, GM, NIGMS

Languages: ENGLISH

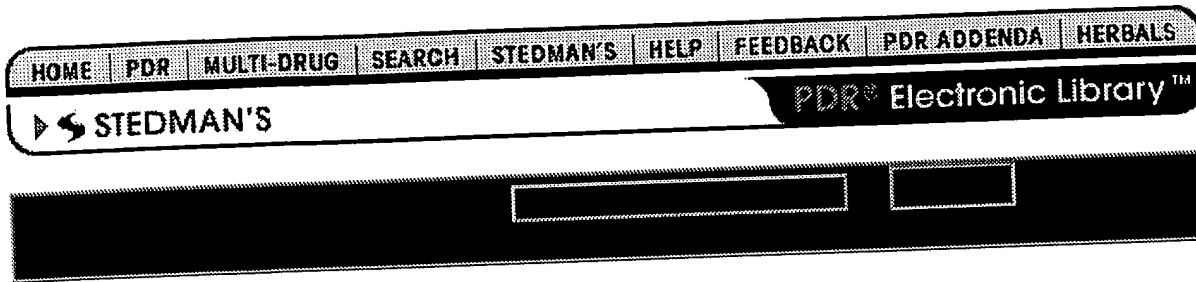
Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 8901

Subfile: INDEX MEDICUS

The dynamic process of embryonic cell motility was investigated by analyzing the lateral mobility of the **fibronectin** receptor in various locomotory or stationary avian embryonic cells, using the technique of fluorescence recovery after **photobleaching**. The lateral mobility of **fibronectin** receptors, labeled by a monoclonal antibody, was defined by the diffusion coefficient and mobile fraction of these receptors. Even though the lateral diffusion coefficient did not vary appreciably ( $2 \times 10^{-10}$  cm<sup>2</sup>/S less than or equal to  $D$  less than or equal to  $4 \times 10^{-10}$  cm<sup>2</sup>/S) with the locomotory state and the cell type, the mobile fraction was highly dependent on the degree of cell motility. In locomoting cells, the population of **fibronectin** receptors, which was uniformly distributed on the cell surface, displayed a high mobile fraction of  $66 \pm 19\%$  at 25 degrees C ( $82 \pm 14\%$  at 37 degrees C). In contrast, in nonmotile cells, the population of receptors was concentrated in focal contacts and fibrillar streaks associated with microfilament bundles and, in these sites, the mobile fraction was small ( $16 \pm 8\%$ ). When cells were in a stage intermediate between highly motile and stationary, the population of **fibronectin** receptors was distributed both in focal contacts with a small mobile fraction and in a diffuse pattern with a reduced mobile fraction ( $33 \pm 9\%$ ) relative to the diffuse population in highly locomotory cells. The mobile fraction of the **fibronectin** receptor was found to be temperature dependent in locomoting but not in stationary cells. The mobile fraction could be modulated by affecting the interaction between the receptor and the substratum. The strength of this interaction could be increased by growing cells on a substratum coated with polyclonal antibodies to the receptor. This caused the mobile fraction to decrease. The interaction could be decreased by using a probe, monoclonal antibodies to the receptor known to perturb the adhesion of certain cell types which caused the mobile fraction to increase. From these results, we conclude that in locomoting embryonic cells, most **fibronectin** receptors can readily diffuse in the plane of the membrane. This degree of lateral mobility may be correlated to the labile adhesions to the substratum presumably required for high motility. In contrast, **fibronectin** receptors in stationary cells are immobilized in focal contacts and fibrillar streaks which are in close association with both extracellular and cytoskeletal structures; these stable complexes appear to provide firm anchorage to the substratum.

Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.



## Stedman's Medical Dictionary

### technetium-99 (<sup>99</sup>Tc)

A radioisotope of technetium which is the decay product of technetium-99m and has a weak beta emission and a physical half-life of 213,000 years.

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USPT	111 not 11	15	<a href="#">L12</a>
USPT	18 same fibronectin	15	<a href="#">L11</a>
USPT	18 and fibronectin	92	<a href="#">L10</a>
USPT	18 and 12	0	<a href="#">L9</a>
USPT	domain near2 b	1157	<a href="#">L8</a>
USPT	ed-b.ab,clm.	0	<a href="#">L7</a>
USPT	ed-b.ti.	0	<a href="#">L6</a>
USPT	edb.ti,ab,clm.	7	<a href="#">L5</a>
USPT	13 not 11	6	<a href="#">L4</a>
USPT	12 and domain.ti,ab,clm.	6	<a href="#">L3</a>
USPT	fibronectin.ti.	84	<a href="#">L2</a>
USPT	(5837813 or 5747452 or 5734025 or 5334711).pn.	4	<a href="#">L1</a>

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## Stedman's Medical Dictionary

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### tin-113 (<sup>113</sup>Sn)

A radioisotope of tin with a physical half-life of 115.1 days; used in the manufacture of radionuclide generators for the production of indium-113m.

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## Stedman's Medical Dictionary

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### radionuclide (ra'de-o-nu'klId)

An isotope of artificial or natural origin that exhibits radioactivity. Radionuclides serve as agents in nuclear medicine and genetic engineering, play a role in computer imaging for diagnosis and experiment, and account for a percentage of background radiation to which humans are exposed. In cancer therapy, radionuclides that localize to certain organs (e.g., radioactive iodine or gallium), deliver cytotoxic radiation doses to tumors. Similarly, radionuclides can be yoked to monoclonal antibodies engineered to attack specific populations of cancerous cells. In positron emission tomography, glucose molecules tagged with radionuclides are injected into the bloodstream. The gamma radiation emitted by the decay of the radionuclides reveals areas of active glucose uptake and thus offers a gauge of cell metabolism and function.

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L1: Entry 4 of 4

File: USPT

Aug 2, 1994

US-PAT-NO: 5334711

DOCUMENT-IDENTIFIER: US 5334711 A

TITLE: Synthetic catalytic oligonucleotide structures

DATE-ISSUED: August 2, 1994

INT-CL: [5] C07H 17/00, C07H 23/00, A01N 43/04, A61K 31/70

US-CL-ISSUED: 536/24.5; 536/23.1, 536/24.3, 536/25.3, 424/2, 935/3

US-CL-CURRENT: 536/24.5; 424/94.1, 435/183, 514/44, 536/23.1, 536/24.3, 536/25.3

FIELD-OF-SEARCH: 536/23.1, 536/24.3, 536/24.5, 536/25.3, 935/3, 514/44, 424/2

**WEST**

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L1: Entry 1 of 4

File: USPT

Nov 17, 1998

US-PAT-NO: 5837813

DOCUMENT-IDENTIFIER: US 5837813 A

TITLE: Fibronectin Type III polypeptides

DATE-ISSUED: November 17, 1998

INT-CL: [6] A61K 38/39, C07K 14/78

US-CL-ISSUED: 530/350; 530/324, 530/380, 530/395

US-CL-CURRENT: 530/350; 530/324, 530/380, 530/395

FIELD-OF-SEARCH: 530/350, 435/69.1

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L1: Entry 2 of 4

File: USPT

May 5, 1998

US-PAT-NO: 5747452

DOCUMENT-IDENTIFIER: US 5747452 A

TITLE: Method of modulating tumor cell migration using fibronectin type III peptides

DATE-ISSUED: May 5, 1998

INT-CL: [6] A61K 38/39, C07K 14/78

US-CL-ISSUED: 514/12; 435/7.24

US-CL-CURRENT: 514/12; 435/7.24

FIELD-OF-SEARCH: 435/7.24, 435/804, 530/811, 424/152.1, 514/12

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L1: Entry 3 of 4

File: USPT

Mar 31, 1998

US-PAT-NO: 5734025

DOCUMENT-IDENTIFIER: US 5734025 A

TITLE: Adsorbent for cellular fibronectin, a method for fractional purification of fibronectin and a method of hemocatharisis

DATE-ISSUED: March 31, 1998

INT-CL: [6] C07K 1/16, C07K 14/745, C08B 5/14

US-CL-ISSUED: 530/417; 530/382, 530/412, 536/56, 536/122

US-CL-CURRENT: 530/417; 530/382, 530/412, 536/122, 536/56

FIELD-OF-SEARCH: 514/8, 514/12, 514/21, 530/380, 530/381, 530/382, 530/412,  
530/415, 530/417, 530/829, 530/830, 530/395, 536/56, 536/122, 536/124, 106/163.1,  
435/2

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USPT	118 and fibronectin	1	<a href="#">L19</a>
USPT	chlorin same photosensitizer	33	<a href="#">L18</a>
USPT	chlorin and photosensitizer	88	<a href="#">L17</a>
USPT	110 same fibronectin	2	<a href="#">L16</a>
USPT	111 and (chimeric or mab or antibodies or immunoglobulin or igg or igm or monoclonal or polyclonal or scfv)	0	<a href="#">L15</a>
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USPT	111 and fibronectin	0	<a href="#">L12</a>
USPT	19 and 110	10	<a href="#">L11</a>
USPT	photo-lysis or photolysis or photosensitive or photosensitizer or photosensitiser or photodynamic or photo-dynamic or photo-sensitizer	59697	<a href="#">L10</a>
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USPT	12 and photo-sensiti\$	0	<a href="#">L5</a>
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USPT	11 and (coagulation near3 factor)	1	<a href="#">L2</a>
USPT	6093399.pn.	1	<a href="#">L1</a>



**Photobleaching of mono-L-aspartyl chlorin e6 (NPe6): a candidate sensitizer for the photodynamic therapy of tumors.**

Spikes JD; Bommer JC

Department of Biology, University of Utah, Salt Lake City 84112.

Photochemistry and photobiology (UNITED STATES) Sep 1993, 58 (3)  
p346-50, ISSN 0031-8655 Journal Code: P69

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9402

Subfile: INDEX MEDICUS

Most sensitizers used for the photodynamic therapy (PDT) of tumors photobleach on illumination. Thus, it is of interest to examine the photobleaching behavior of new sensitizers proposed for use in PDT. This report surveys the quantum yields and kinetics of the photobleaching of mono-L-aspartyl chlorin e6 (NPe6), a hydrophilic chlorin that has many of the photoproperties desirable in a sensitizer for clinical PDT. It is a very effective sensitizer for the PDT of several types of model tumors in animals and is now in Phase I clinical trials. The quantum yield of NPe6 photobleaching in pH 7.4 phosphate buffer in air was  $8.2 \times 10^{-4}$ ; this is greater than the yields for typical porphyrin photosensitizers. For example, the yields for hematoporphyrin and uroporphyrin are  $4.7 \times 10^{-5}$  and  $2.8 \times 10^{-5}$ , respectively. The yield decreased significantly in organic solvents of low dielectric constant. The Sn derivative of NPe6 was more light stable than NPe6 (yield =  $5.7 \times 10^{-6}$ ), while the Zn derivative was more sensitive (yield =  $1.9 \times 10^{-2}$ ). Oxygen appeared to be necessary for the photobleaching of NPe6; however, bleaching was not inhibited by 100 mM azide, an efficient quencher of singlet oxygen. The photooxidizable substrates cysteine, dithiothreitol and furfuryl alcohol increased the quantum yield of photobleaching two- to four-fold, while the electron acceptor, metronidazole, increased it almost six-fold. Photobleaching yields for several other chlorins were also measured.

Tags: Animal; Human; Support, Non-U.S. Gov't

Descriptors: \*Antineoplastic Agents--Chemistry--CH;

**Control of hypertrophic scar growth using antibody-targeted photolysis.**

Wolfort SF; Reiken SR; Berthiaume F; Tompkins RG; Yarmush ML

Surgical Services, Massachusetts General Hospital, Boston, 02114, USA.

Journal of surgical research (UNITED STATES) Apr 1996, 62 (1) p17-22,  
ISSN 0022-4804 Journal Code: K7B

Contract/Grant No.: T32-GM07350, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9607

Subfile: INDEX MEDICUS

Hypertrophic scar is marked by excess collagen accumulation secondary to an increased vascularization response in the scar and an increase in fibroblast cell density. It is currently the most debilitating long-term complication of the surviving burn patient, and at present, there is no routinely effective form of therapy. In this study, we investigated the potential use of antibody-targeted photolysis (ATPL) in treating hypertrophic scars. An immunoconjugate consisting of a photosensitizer (Sn - chlorin e6) linked to a monoclonal antibody that binds to human myofibroblasts (PR2D3) was prepared, which in response to photoactivation produces singlet oxygen in close proximity to the target cell surface. The model used for these studies consisted of 1-mm 3 human hypertrophic scar tissue implants in athymic mice. These implants increase approximately 20-fold in volume over a period of 15 days. Four days after implantation immunoconjugate was injected directly into scar implants allowed to diffuse throughout for 24 hr before implants were illuminated with laser light at 630 nm (120 J/cm<sup>2</sup>). ATPL treatment caused a significant reduction in total growth compared to the untreated controls (P < 0.05). No effect was observed when an irrelevant conjugate (anti-Pseudomonas aeruginosa) was used. Histological examination of the ATPL-treated implants 24 hr post-ATPL revealed the presence of a large number of lipid droplets indicative of massive cell damage and infiltration by mononuclear cells and neutrophils.

Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

**Purpurins and benzochlorins as sensitizers for photodynamic therapy.**

Garbo GM

Department of Chemistry, University of Toledo, OH 43606, USA.

Journal of photochemistry and photobiology. B, Biology (SWITZERLAND)

Jul 1996, 34 (2-3) p109-16, ISSN 1011-1344 Journal Code: JLI

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

JOURNAL ANNOUNCEMENT: 9702

Subfile: INDEX MEDICUS

Purpurins and benzochlorins are hydrophobic second generation photosensitizers, which have sizable absorption in the 650-780 nm range and exhibit photodynamic activity against tumors after visible light treatment. This review summarizes the published data regarding these compounds: from the spectroscopic, photophysical and photochemical characteristics to the in vivo and in vitro photodynamic inactivation of tumors and normal tissue effects. Some mechanistic studies using both the **Sn**-etiopurpurin and/or the Cu-benzochlorin derivatives are also reviewed. (64 Refs.)

Tags: Animal; Human

Descriptors: \*Lectins--Therapeutic Use--TU; \*Photochemotherapy; \*Photosensitizing Agents--Therapeutic Use--TU; \*Porphyrins--Therapeutic Use--TU; Drug Administration Routes; Lectins--Chemistry--CH; Photochemistry; Photosensitizing Agents--Chemistry--CH; Porphyrins--Chemistry--CH

CAS Registry No.: 0 (purpurin); 0 (Lectins); 0 (Photosensitizing Agents); 0 (Porphyrins); 2683-84-3 (chlorin)

**Control of fibroblast populated collagen lattice contraction by antibody targeted photolysis of fibroblasts.**

Strong LH; Berthiaume F; Yarmush ML

Center for Engineering in Medicine/Surgical Services, Massachusetts General Hospital, Boston 02114, USA.

Lasers in surgery and medicine (UNITED STATES) 1997, 21 (3) p235-47,  
ISSN 0196-8092 Journal Code: L1X

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9801

Subfile: INDEX MEDICUS

**BACKGROUND AND OBJECTIVE:** Hypertrophic scarring and rigid scar contracture are disorders of wound healing for which there is presently no effective therapy. The dermal fibroblast plays a major role in scar fibrillogenesis and contracture. The objective of this study was to establish a selective and effective method to destroy fibroblasts. **STUDY DESIGN/MATERIALS AND METHODS:** An antifibroblast conjugate was synthesized by covalent attachment of the antifibroblast antibody PR2D3 to the photosensitizer Sn - chlorin e6. Fibroblasts were cultured in fibroblast-populated collagen lattices (FPCLs), incubated with the conjugate and exposed to light. The effect of the treatment on cell viability and the rate of contraction of the FPCL were assessed. **RESULTS:** The toxicity of antifibroblast conjugates increased with increasing conjugate concentration, light dose, and number of photosensitizers per antibody molecule, until nearly complete killing was achieved. The rate of lattice contraction after irradiation linearly correlated with the remaining viable fraction of fibroblasts. These conjugates were not cytotoxic to keratinocytes cultured on collagen lattices, and nonspecific conjugates could not cause significant fibroblast killing. Spatial selectivity was demonstrated using a light mask. **CONCLUSIONS:** Antibody-targeted photolysis is an effective and selective technique for controlling FPCL contraction in vitro and may have potential in vivo applications to modulate extracellular matrix remodeling by connective tissue cells.

Tags: Animal; Human; Support, Non-U.S. Gov't

**Photodynamic therapy inhibits cell adhesion without altering integrin expression.**

Margaron P; Sorrenti R; Levy JG

QLT PhotoTherapeutics Inc., Vancouver, Canada. pmargaro@qlt-pdt.com

Biochimica et biophysica acta (NETHERLANDS) Dec 12 1997, 1359 (3)

p200-10, ISSN 0006-3002 Journal Code: AOW

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9804

Subfile: INDEX MEDICUS

Adhesion is a primordial cell function that, among others, regulates inflammation, metastasis, and tissue repair. To understand how these events could be affected by **photodynamic** therapy (PDT), we studied the effects of PDT on human foreskin fibroblast (HFF) adhesion to bovine collagen type I, human vitronectin or **fibronectin**. PDT, using benzoporphyrin derivative monoacid ring A (verteporfin) as the **photosensitizer**, inhibited cell adhesion in a drug dose-dependent manner, with no significant difference among matrices. The drug dose that killed 90% of cells within 20 h post-treatment inhibited HFF adhesion by 55%-68%. However, 45 min following PDT, a time period corresponding to that of the adhesion assay, HFF membrane integrity remained unaltered. In addition, cell surface expression of integrins was not modified for at least 2h following PDT. Western blots of cell lysates, using the anti-phosphotyrosine 4G10 monoclonal antibody, revealed that PDT prevented the adhesion-induced phosphorylation of 110-130 kDa proteins. Immunoblots of cell lysates immunoprecipitated with antibodies to focal adhesion kinase suggested that its phosphorylation was suppressed by PDT. These results demonstrate that PDT inhibits cell adhesion and affects integrin signalling without modifying cell membrane integrity or integrin expression.

Tags: Animal; Human

**Photodynamic therapy of extracellular matrix stimulates endothelial cell growth by inactivation of matrix-associated transforming growth factor-beta.**

Stattius van Eps RG; Adili F; Watkins MT; Anderson RR; LaMuraglia GM  
Division of Vascular Surgery, Massachusetts General Hospital, Harvard Medical School, Boston.

Laboratory investigation (UNITED STATES) Feb 1997, 76 (2) p257-66,  
ISSN 0023-6837 Journal Code: KZ4

Contract/Grant No.: HL02583, HL, NHLBI; HL 48152, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9705

Subfile: INDEX MEDICUS

**Photodynamic** therapy (PDT), the production of cytotoxic free-radical moieties by light activation of **photosensitizer** dyes, is a novel approach to inhibit experimental intimal hyperplasia. Local eradication of vascular cells with this method in vivo is followed by expedient reendothelialization, and PDT of extracellular matrix (ECM) in vitro stimulates endothelial cell (EC) growth. This in vitro study explored one possible mechanism underlying these findings by investigating the effects of PDT on matrix-associated transforming growth factor-beta (TGF-beta), a potent inhibitor of EC growth. The ECM deposited by EC on tissue culture plates contained  $85.4 \pm 10.2$  pg/10 cm<sup>2</sup> of TGF-beta, as measured by an ELISA. In contrast, after PDT of ECM, levels of TGF-beta could be barely be detected ( $0.2 \pm 0.5$  pg/10 cm<sup>2</sup>). The functional consequence of this observation was demonstrated by the finding that PD1 of plates coated with a **fibronectin** -TGF-beta complex stimulated EC mitogenesis ( $102.3\% \pm 19.3\%$ ,  $p < 0.0005$ ) compared with the untreated control ( $44.1\% \pm 13.5\%$ ). The inhibitory effect of ECM-associated TGF-beta on EC was further delineated by blocking its activity with a specific antibody. Whereas the antibody did not affect EC mitogenesis or PDT-treated matrix or matrix-free plates ( $101\% \pm 8.8\%$ ,  $105.6\% \pm 9.8\%$ ), EC mitogenesis growing on ECM was significantly enhanced ( $125.9\%$ ,  $17.5\%$ ,  $p < 0.05$ ). Finally, SDS-PAGE analysis of PDT-treated TGF-beta in solution demonstrated that the PDT-mediated loss of TGF-beta activity was not associated with changes in its molecular weight. These data demonstrate that increased EC proliferation on PDT-treated matrix is, at least in part, mediated by inactivation of TGF-beta. PDT-removal of this EC growth inhibitor in the intima provides a mechanism by which PDT of the vascular wall could potentiate endothelial regrowth, a factor which may promote proper healing and result in the inhibition of intimal hyperplasia.

**Incorporation of fluorescent gangliosides into human fibroblasts: mobility, fate, and interaction with fibronectin.**

Spiegel S; Schlessinger J; Fishman PH

Journal of cell biology (UNITED STATES) Aug 1984, 99 (2) p699-704,  
ISSN 0021-9525 Journal Code: HMV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 8411

Subfile: INDEX MEDICUS

Rhodamine- and fluorescein-labeled gangliosides were used as probes to investigate the distribution, dynamics, and fate of plasma membrane-bound gangliosides on cultured human fibroblasts. When sparse cultures of fibroblasts were incubated with the fluorescent ganglioside derivatives, their surfaces became highly fluorescent. The fluorescent gangliosides were taken up by the cells in a time- and temperature-dependent manner and were not removed from the cell surface by trypsin or serum. Thus, the gangliosides appeared to be stably incorporated into the lipid bilayer of the plasma membrane. Fluorescent **photobleaching** recovery measurements showed that the inserted gangliosides were free to diffuse in the plane of the membrane with a high diffusion coefficient of approximately  $10(-8)$  cm<sup>2</sup>/s. When the ganglioside-treated cells were washed and incubated in fresh medium, the surface gangliosides became internalized with time, and localized in the perinuclear region of the fibroblasts. In dense cultures of fibroblasts, a large fraction of the fluorescent gangliosides were organized in a fibrillar network and were immobile on the time scale of fluorescent **photobleaching** recovery measurements. Using antifibronectin antibodies and indirect immunofluorescence, these gangliosides were found to co-distribute with fibrillar **fibronectin**. Thus, exogenous gangliosides appear to be stably inserted into the lipid bilayer of the plasma membrane and to diffuse freely in its plane as well as form a less mobile state with the fibrillar networks of **fibronectin** associated with the cells.

Tags: Human; Male

**A new radioactive cross-linking reagent for studying the interactions of proteins.**

Schwartz MA; Das OP; Hynes RO

Journal of biological chemistry (UNITED STATES) Mar 10 1982, 257 (5)  
p2343-9, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 8207

Subfile: INDEX MEDICUS

We have developed a photoactivable, heterobifunctional, reversible, radioactively labeled, chemical cross-linking reagent, 3-[(2-nitro-4-azidophenyl)-2-aminoethyldithio]-N-succinimidyl propionate, for studying the interactions of proteins in situ. When reacted in the dark with a purified protein, it forms a covalent derivative which can be purified and reconstituted into biological systems. This derivative will form cross-links to neighboring macromolecules only upon **photolysis**; reduction cleaves the cross-link and transfers the radiolabel to the second molecule, which can then be identified by standard techniques. We have tested the cross-linker using the binding of gelatin to **fibronectin**. The cross-linker gives the proper chemical behavior under biological conditions, reacts with high yield and with a very low level of nonspecific cross-linking, and can be used to identify protein-protein and other interactions at the cell surface and elsewhere. The advantages, limitations and possible uses for this reagent are discussed.



Antibody specific for extra domain B of fibronectin demonstrates elevated levels of both extra domain B(+) and B(-) fibronectin in osteoarthritic canine cartilage.

Zang DW; Burton-Wurster N; Lust G

James A. Baker Institute for Animal Health, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA.

Matrix biology (GERMANY) Oct 1995, 14 (8) p623-33, ISSN 0945-053X

Journal Code: BOT

Contract/Grant No.: AR35664, AR, NIAMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9705

Subfile: INDEX MEDICUS

A fusion protein containing the alternately spliced Extra Domain B [ED-B(+)] sequence of canine fibronectin was expressed in E. coli and the purified protein was used to produce an antibody specific for the ED-B (+) segment. This **antibody** recognized canine cartilage **fibronectin** but not canine plasma or synovial fluid **fibronectin**. Using this **antibody**, it was determined that **ED -B (+) fibronectin** increased proportionally with the total **fibronectin** in osteoarthritic cartilage. From this result, it was concluded that the chondrocyte is the source of much of the elevated **fibronectin** that appears in osteoarthritic cartilage.

Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

High levels of fibronectin in the stroma of aural cholesteatoma.

Schilling V; Holly A; Bujia J; Schulz P; Kastenbauer E

Department of Otorhinolaryngology, Head and Neck Surgery, Grosshadern Medical Center, Ludwig-Maximilians-University, Munich, Germany.

American journal of otolaryngology (UNITED STATES) Jul-Aug 1995, 16 (4) p232-5, ISSN 0196-0709 Journal Code: 32W

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

JOURNAL ANNOUNCEMENT: 9601

Subfile: INDEX MEDICUS

PURPOSE: Because abundant **fibronectin** deposition is a hallmark of healing cutaneous wounds and provides a matrix for hyperproliferative and migratory epidermal cells, the distribution of **fibronectin** in aural cholesteatoma was investigated immunohistochemically. MATERIALS AND METHODS: A **monoclonal antibody** against the major cell binding **domain** of human **fibronectin** was used to stain 4-micron cryosections of cholesteatoma tissue by the alkaline phosphatase-antialkaline phosphatase method. Section of normal retroauricular skin served as control. RESULTS: When processed in parallel, **fibronectin** staining was much stronger in the stroma of cholesteatoma than in normal dermis. The squamous epithelium of both tissues did not show any staining for **fibronectin**. CONCLUSIONS: These observations lend support to the view that the growth of cholesteatoma epithelium reflects an aberrant regenerative process. (28 Refs.)

Human keratinocytes adhere to and spread on synthetic peptide FN-C/H-V derived from fibronectin.

Wilke MS; Vespa J; Skubitz AP; Furcht LT; McCarthy JB

Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis 55455-0315.

Journal of investigative dermatology (UNITED STATES) Jul 1993, 101 (1) p43-8, ISSN 0022-202X Journal Code: IHZ

Contract/Grant No.: NCI CA08843, CA, NCI; NCI CA21463, CA, NCI; NCI CA43924, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9310

Subfile: INDEX MEDICUS

In a previous study, we reported that two synthetic peptides derived from the 33-kD carboxyl terminal cell/heparin-binding fragment of **fibronectin** A chain promoted keratinocyte adhesion but not spreading. Because keratinocytes are capable of spreading on the 33/66-kD fragments, we focused on identifying additional chemically synthesized peptides from the cell/heparin-binding fragments of **fibronectin** that might promote cell spreading. When plastic substrata were coated with peptide FN-C/H-V (WQPPRARI), which is derived from the carboxyl-terminal heparin-binding **domain** of all plasma **fibronectin** isoforms, keratinocytes adhered and displayed a spread morphology. In solution, soluble peptide FN-C/H-V inhibited cell spreading on intact **fibronectin** and on the 33/66-kD fragments. Furthermore, **polyclonal antibodies** raised against peptide FN-C/H-V also inhibited keratinocyte spreading on **fibronectin** and the 33/66-kD fragments. These data support the hypothesis that keratinocyte cell adhesion and cell spreading on **fibronectin** are mediated by multiple distinct **domains** and different regulatory processes.

**Increased fragmentation of urinary fibronectin in cancer patients detected by immunoenzymometric assay using domain-specific monoclonal antibodies.**

Katayama M; Kamihagi K; Nakagawa K; Akiyama T; Sano Y; Ouchi R; Nagata S; Hino F; Kato I

Biotechnology Research Laboratories, Takara Shuzo Co., Ltd., Shiga, Japan.

Clinica chimica acta; international journal of clinical chemistry (NETHERLANDS) Aug 31 1993, 217 (2) p115-28, ISSN 0009-8981

Journal Code: DCC

Languages: ENGLISH

Document type: JOURNAL ARTICLE

JOURNAL ANNOUNCEMENT: 9403

Subfile: INDEX MEDICUS

**Monoclonal antibodies** (MoAbs) recognizing the distinct **domains** of human **fibronectin** had previously been established and they were used to construct several sandwich immunoenzymometric assays (IEMAs) for the structural analysis of **fibronectin** found in the urine of cancer patients. Urinary **fibronectin** (UFN) was immunodetectable only with FN12-8 and FN30-8 MoAbs against cell-binding domains and was less reactive with other IEMAs using MoAbs directed to terminal domains, indicating that UFN was almost completely fragmented and consisted mainly of cell-binding regions. The IEMA using MoAbs against cell-binding domains had sufficient immunoreactivities with the antigen fragmented by artificial proteolysis, but these fragments could hardly be detected by other IEMAs. UFN levels were significantly elevated in various cancer patients and extremely elevated in some patients with distant metastasis. It is presumed that UFN fragments which increase in cancer patients are generated by extracellular matrix destruction. Thus UFN levels and the ratio of the fragmented UFN level to the non-fragmented UFN level appear to be informative clinical indicators of tumor malignancy or metastatic ability in cancer patients.

Tags: Animal; Human

Descriptors: **Fibronectins** --Urine--UR; \*Neoplasms--Urine-